containing a contiguous sequence of at least [an] 25 nucleotides [portion] of SEQ ID NO:38.

29. A diagnostic kit, comprising in one or more containers, a pair of primers, each having at least 15-25 nucleotides, in which at least one of said primers is hybridizable, under stringent conditions, to SEQ. ID. NO: 38 or its complement and wherein said primers are capable of priming DNA synthesis in a nucleic acid amplification reaction.

Remarks

The Examiner has objected to the disclosure having references to 10 Figures, where only 4 were filed with the Application. The Applicant has corrected this by providing herein all 10 Figures. No new matter has been added, as the description of Figures 5-10 is detailed in the Specification under the heading of Description of the Drawings, as well as throughout the Detailed Description of the Invention. The figures represent a pictorial presentation of what is already described in the Application, as originally filed.

Claims 1-5, 8-16, 22-24, and 29 are pending in the current application. Claims 2-5, 8, 10-16, 23 and 29 have been amended. Reconsideration and allowance of the claims is respectfully requested in view of the above changes and the following Remarks.

I. §112, second paragraph Rejection of Claims 1-5, 8-16, 22-24, and 29.

The Examiner states "it is not clear from applicant's disclosure whether the *TCL-1b* gene encompasses only the gene consisting of the sequence of SEQ ID NO:40 or whether other genes are encompassed. Furthermore, if additional gene products are encompassed within the definition of a Tcl-1b protein, the disclosure does not appear to teach the

metes and bounds of these genes. Therefore, the metes and bounds of the claimed invention cannot be determined and the claims are indefinite." The Applicant has amended claims 2-5, 8, 10-16, 23 and 29 to more clearly describe the invention. The following paragraphs will address the Examiner's rejections.

Claims 2, 5, and 11 encompass the entire referenced sequence

Claim 2 has been amended to recite "said nucleotide sequence encodes a human Tcl-1b protein having amino acid sequence SEQ. ID. NO: 39 from amino acid number 1 to 128." Also, claim 5 has been amended to more clearly state that "The isolated nucleic acid of claim 1, comprising nucleotide sequence SEQ. ID. NO: 38 from nucleotide number 1 to 1152." Claim 11 has been amended to "having amino acid sequence SEQ. ID. NO: 39 from amino acid number 1 to 128." Deletion of "a/an" and "of" in the claims results in claims that more clearly and distinctly claim that which the Applicant regards as his invention: the isolated nucleic acid encoding the Tcl-1b protein (SEQ. ID. NO: 39); an isolated nucleic acid of SEQ. ID. NO: 38 from nucleotide 1 to 1152 which encodes the Tcl-1b protein; and the recombinant DNA vector containing a nucleotide sequence encoding human Tcl-1b protein having an amino acid sequence SEQ. ID. NO: 39 from amino acid 1 to 128.

The metes and bounds of the claimed invention

Claim 8 has been amended to more clearly and distinctly claim that which the Applicant regards as his invention, specifically an isolated nucleic acid comprising a sequence encoding a fragment of the Tcl-1b protein, which protein is defined as the sequence of amino acids depicted in SEQ. ID. NO: 39. The Examiner states that "It is not clear if the claims are intended to encompass the entire referenced sequence or whether the claims also encompass some undefined portion thereof."

The Applicant respectfully disagrees. The term "fragment" is defined on page 25, lines 26-32 to page 26, lines 1-9. A gene encoded Tcl-1b protein fragment is one that displays "one or more biological activities associated with

the full-length protein[s]. Such biological activities include, but are not limited to, antigenicity . . . and immunogenicity . . . ." Furthermore, the structure of the gene encoded Tcl-1b fragments are defined as "consisting of at least 10 amino acids . . . sharing at least 70% amino acid homology . . . to the naturally occurring Tcl-1b protein over at least 25 contiguous amino acids. . . ."

Thus, the Applicant has delineated the boundaries which define the gene encoded Tcl-1b "fragment" (*supra*), thereby "teach[ing] the metes and bounds of these gene[s] products." Additionally, "homology" is defined on page 26, lines 4 to 6 as "amino acid sequences having identical amino acid residues or amino acid sequences containing conservative changes in amino acid residues." Conservative changes are silent changes, changes in an amino acid residue(s) wherein a significant degree of sequence similarity exists between the amino acid(s) in a Tcl-1b fragment and the amino acid(s) in the Tcl-1b protein (SEQ ID NO: 39) such that the function of the protein/peptide fragment is not altered, i.e. it retains the function of the parent protein, the Tcl-1b protein (SEQ. ID. NO: 39). The Examiner is referred to page 33, lines 9 to 11 wherein a "silent change" in an amino acid is "made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residue(s) involved." These changes are well within the skill of those knowledgeable in the art.

A nucleotide "portion" is a contiguous nucleotide sequence

Claim 3 has been amended to claim "a contiguous sequence of at least 18 nucleotides encoding a Tcl-1b protein fragment." Additionally, claims 4, 12, 14, and 23 have been amended to claim "a contiguous sequence of at least . . . nucleotides of . . .".

The amendment clearly defines that the nucleotide sequence is "contiguous," thereby clarifying any ambiguity that may have existed. The deletion of "portion" and "an" in the aforementioned claims results in a clear and distinct definition of the claimed invention.

The *TCL-1b* gene encompasses the sequence SEQ. ID. NO: 40

The Examiner states that it is not clear whether the *TCL-1b* gene encompasses only the gene consisting of the sequence of SEQ. ID. NO: 40, or if other genes are also encompassed by SEQ. ID. NO: 40 (*supra*). Claims 4 and 12, which refer to SEQ. ID. NO: 40, claim a nucleic acid with at least 18 nucleotides or 50 nucleotides, respectfully, of SEQ. ID. NO: 40. This sequence is not an "other gene." The contiguous sequence of at least 18 or 50 nucleotides of SEQ. ID. NO: 40, the *TCL-1b* gene, is a contiguous sequence of nucleotides within an isolated nucleic acid, of which the sequence is shown in SEQ. ID. NO: 40. It is well within the knowledge of those skilled in the art to understand that the gene consisting of the sequence of SEQ. ID. NO: 40 is the only gene encompassed by the human *TCL1b* gene. Furthermore, those skilled in the art could readily envision an isolated nucleic acid with at least 18 or 50 contiguous nucleotides of the *TCL1b* gene (SEQ. ID. NO: 40), as the entire sequence of the *TCL-1b* gene (SEQ. ID. NO: 40) is disclosed in the current application.

In the specification on page 14, lines 16-18 of the application, as filed, the Applicant discloses "a ~1.2 kb full length cDNA (SEQ. ID. NO: 38) was isolated . . . encodes a 14 kDa protein of 128 amino acids (SEQ. ID. NO: 39)." Further on page 14, line 32 to page 15, line 1, the Applicant states that the *TCL1b* gene (SEQ. ID. NO: 40) is 6.5 kb in size and contains 4 exons. The Applicant also discloses how the gene was isolated (page 14 under the heading "Identification of the *TCL1b* gene") and how its chromosomal location was mapped (page 14, lines 23-24) and its size, number of exons and ATG start site determined (page 14, line 32 to page 15, line 1 and page 14, lines 19-20). Therefore, the Applicant has clearly disclosed that the *TCL-1b* gene encompasses the gene consisting of the sequence SEQ. ID. NO: 40, which encodes the 128 amino acid Tcl-1b protein consisting of sequence SEQ. ID. NO: 39. A contiguous sequence of nucleotides contained within SEQ. ID. NO: 40, claims 4 and 12, is just that, a sequential number of nucleotides, for example "at least 18 (or 50)" as disclosed in the present invention, within the sequence of, the *TCL-1b* gene.

Stringent hybridization conditions

Claims 13, 14, and 23, are drawn to an isolated nucleic acid capable of hybridizing under "stringent" conditions. The Examiner states that "[t]he disclosure fails to teach the metes and bounds of 'stringent' conditions. Therefore, . . . claims are indefinite." The Applicant respectfully disagrees.

The Examiner is directed to page 29, line 26 through page 30, line 6 wherein the Applicant has disclosed that "[t]he phrase 'stringent conditions' as used herein refers to those hybridizing conditions that employ . . . ." The disclosure details the ionic strength, temperature, use of a denaturing agent, sonicated sperm DNA, SDS and dextran sulfate. Furthermore, the Applicant has supplied a number of references, which are at least four years old, implying that "stringent conditions" are conditions that have been well established in the art, and are, therefore, well known to those of skill in the art.

There is not one specific method of designing a "stringent condition." The Applicant has supplied an example of a stringent condition wherein only those nucleic acid sequences sharing substantial sequence homology to *TCL1b* will hybridize to *TCL1b*. "In reviewing a claim for compliance with 35 U.S.C. 112, second paragraph, the examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope, and therefore, serves the notice function required by 35 U.S.C. 112, second paragraph." *Solomon v. Kimberly-Clark Corp.,* 216 F.3d 1372, 1379, 55 USPQ2d 1279, 1283 (Fed. Cir. 2000); see also *In re Larsen,* No. 01-1092 (Fed. Cir. May 9, 2001). The disclosure of the "stringent conditions" used, as well as references to aid in the determination of alternative "stringent conditions", clearly and precisely teaches the "metes and bounds" of the invention.

Nucleotide sequences complementary to nucleic acids encoding Tcl-1b form stable duplexes

On page 64, lines 8 to 10 the disclosure states that the phrase "at least a part (or portion) of" is meant to refer to "a sequence having sufficient complementarity to be able to hybridize . . . forming a stable duplex". Claim 15 has been amended to claim a "nucleotide sequence complementary to at least

six nucleotides of coding sequence . . . which forms a stable duplex *in vivo* with a Tcl-1b mRNA." This clarifies the "at least a part" by defining "part" as being at least a six nucleotide sequence within the Tcl-1b coding sequence. It is well within the skill of those knowledgeable in the art to make an antisense molecule complementary to at least six nucleotides of coding sequence in the Tcl-1b mRNA (SEQ. ID. NO:38, the Tcl-1b cDNA) (see page 57, lines 14 - 24 and page 63, lines 4-10 wherein examples of the preparation of antisense nucleic acids and of the synthesis of oligonucleotides are disclosed).

Additionally, "is hybridizable" has been replaced with "forms a stable duplex *in vivo* with" (disclosed in the specification on page 64, lines 9-10). The specific conditions under which hybridization, the formation of a stable duplex, occurs are those that occur *in vivo*. The *in vivo* conditions are met upon the delivery of a pharmaceutical composition containing the antisense molecule (page 62, lines 6-8). Alternatively, the antisense molecule is produced upon the *in vivo* transcription of an exogenous sequence (page 63, lines 17-32 through page 64, lines 1-3). It is well known in the art that hybridization of the antisense nucleic acid to its target mRNA occurs such that gene expression is inhibited (*infra*).

Claim 16 has also been amended to more clearly and distinctly claim that which is the Applicant's invention. Thus, "a part" has been amended to recite "six nucleotides" to clarify the length of the minimum required target sequence.

Claim 29 has been amended to define the hybridization conditions. The primer hybridizes to its target site under stringent conditions. Such conditions are well known to those of skill in the art and are defined on page 29, lines 25-32 through page 30, lines 1-6. As disclosed on page 29, lines 25-32 through page 30, lines 1-6 in the present invention, stringent conditions employ low ionic strength and high temperature for washing, as well as the optional inclusion of a denaturing agent.

It is the Applicant's belief that claims 1, 9, 22 and 24 and amended claims 2-5, 8, 10-16, 23, and 29 distinctly claim the subject matter which the Applicant regards as the application, as defined by 35 U.S.C. §112, paragraph two, and the

Applicant respectfully requests reconsideration of claims 1, 9, 22 and 24 and amended claims 2-5, 8, 10-16, 23 and 29.

II. §112, first paragraph Rejection of Claim 8.

The Examiner states that claim 8 "contain[s] subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a 'written description' rejection." Claim 8 has been amended (*supra*). The Applicant will respond to the Examiner's rejection of claim 8 in light of the amended claim 8.

Written description of what is being claimed

The Examiner cites the Federal Circuit as stating that "[a]n adequate written description of DNA ... requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed invention." According to the Examiner

> "[t]here is a single species of the claimed genus disclosed that is within the scope of the claimed genus, *i.e.* the Tcl-1b protein consisting of amino acids 1-128 of SEQ ID NO: 39. . . . However, the present claim encompasses numerous species that are not further described. There is substantial variability among the species. One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genus of which comprises a myriad of possible fragments of the Tcl-1b protein, as well as the full length protein. The skilled artisan cannot envision the detailed chemical structure of the encompassed fragments."

Claim 8 has been amended to more clearly define what is meant by "fragment." The amended claim recites an "isolated nucleic acid comprises a sequence encoding a fragment of a protein having an amino acid sequence of at least 10 amino acids, sharing at least 70% amino acid homology to at least 25 contiguous amino acids of SEQ ID NO: 39." Support for amended claim 8 is found on page 25, lines 18-32 through page 26, lines 1-9.

"For some biomolecules, examples of identifying characteristics include a sequence, structure, binding affinity, binding specificity, molecular weight and

length. Although structural formulas provide a convenient method of demonstrating possession of specific molecules, other identifying characteristics or combinations of characteristics may demonstrate the requisite possession . . . [and] be sufficient to show possession of the claimed invention to one of skill in the art." MPEP 2163. "One must define a compound by 'whatever characteristics sufficiently distinguish it.' " *Pfaff v. Wells Electronics, Inc.*, 525, U.S. 55, 68, 119 S. Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Eli Lilly,* 119 F.3d at 1568, 43 USPQ2d at 1406; *Amgen, Inc. v. Chugai Pharmaceutical,* 927, F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991). The Applicant has disclosed the identifying characteristics of sequence, molecular weight, length, and structural properties. The structural properties that define what a Tcl-1b fragment comprises are defined in amended claim 8. Support for such structural limitations are delineated on page 25, lines 26-32 through page 26, lines 1-9 of the present application. The arrangement of the parts of the fragment, i.e. the structure, constitute a portion of the amino acid sequence, which is supplied in SEQ ID NO: 39.

The disclosure of the sequence of the Tcl-1b protein clearly shows that the Applicant was in possession of the invention at the time the application was filed. Furthermore, it is standard molecular biology, and thus well known to those of skill in the art, how to make a protein fragment of "at least 10 amino acids . . . sharing at least 70% amino acid homology . . . over at least 25 contiguous amino acids of the Tcl-1b amino acid sequence," which amino acid sequence is supplied in the current application as SEQ ID NO: 39. The Applicant has disclosed examples of methods by which to synthesize the Tcl-1b protein (page 34, lines 4-16), in whole or in part. Finally, "at least 25 contiguous amino acids of the Tcl-1b amino acid sequence" is supplied within the 128 amino acid sequence of SEQ ID NO: 39.

In addition to the structural properties of a Tcl-1b fragment, the Applicant has disclosed the "physical propert[y]ies" of the Tcl-1b protein fragment (page 25, lines 18-25). The application discloses that a "fragment or amino acid variant of the Tcl-1b protein (SEQ ID NO: 39) must display one or more biological activities associated with the full-length protein[s]. Such biological activities include, but are not limited to, antigenicity . . . and immunogenicity."

Disclosure of the species encompassed by the genus

The Examiner states ". . . the present claim encompasses numerous species that are not further described. There is substantial variability among the species." The Applicant has described (*supra*) the requirements that a Tcl-1b fragment, i.e. a species, must possess. While these requirements allow for a number of species to exist, it is well within those of skill in the art to envision such species. The only variability that could exist between the species is the amino acid sequence and/or the length of the amino acid sequence. The physical properties (*supra*) are the same. A "species" is a group that has common attributes. The common attributes that a fragment must have in order to be included as a "species" (*supra*) are described in the present application on page 25, lines 18-32 through page 26, lines 1-9. Thus, the Applicant has clearly supplied "an adequate written description," as defined by §112, paragraph one.

"An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using [such] descriptive means . . . ". *Lockwood v. American Airlines, Inc.,* 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). "Possession may be shown in a variety of ways including . . . describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention." *Pfaff v. Wells Electronics, Inc.,* 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); see also *Eli Lilly,* 119 F.3d at 1568, 43 USPQ2d at 1406; *Amgen, Inc. v. Chugai Pharmaceutical,* 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991).

The Applicant has defined both the structural and physical requirements of the Tcl-1b protein fragment, thereby supplying the distinguishing characteristics of the fragment. This information, along with the 128 amino acid sequence of the Tcl-1b protein, as defined in SEQ ID NO: 39, clearly demonstrates that the Applicant was in possession of the invention as of the filing date. The written description (see page 25, lines 18-32 through page 26, lines 1-9) allows those skilled in the art to envision the claim (i.e., a Tcl-1b fragment). As stated by the Examiner in the Official Action "A description of a genus may be achieved by means of a recitation of . . . structural features common to the members of the

genus, which features constitute a substantial portion of the genus." The Applicant has clearly described such "structural features."

"There is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed." *Wertheim*, 541 F.2d at 262, 191 USPQ at 96. "Consequently, a rejection of an original claim for lack of written description should be rare". MPEP §2163. It is the Applicant's belief that claim 8 contains subject matter which is described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention, as defined by 35 U.S.C. §112, paragraph one. The Applicant respectfully requests reconsideration of amended claim 8.

II. §112 first paragraph Rejection of Claims 1-5, 8-16, 22-24, and 29

The Examiner states that "[c]laims 1-5, 8-16, 22-24, and 29 . . .contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." The Applicant has amended claims 2-5, 8, 10-16, 23 and 29 (*supra*). The Applicant will respond to the Examiner's rejection in light of amended claims 2-5, 8, 10-16, 23 and 29 and claims 1, 9, 22 and 24.

The *TCL-1b* gene is activated by chromosomal rearrangements

The Examiner has cited Pekarsky et al. as "teach[ing] that the *TCL1b* gene is expressed . . . in tissues other than malignancies . . .." The Examiner is correct in stating that the *TCL-1b* gene is expressed in "tissues other than malignancies," i.e. normal tissues. While the *TCL-1b* gene is expressed in normal tissues, the expression level is quite low. As noted in the specification, the expression profile of the *TCL-1b* gene is such that *TCL-1b* is expressed at very low levels in normal bone marrow and peripheral blood lymphocytes (page 4, lines 13-21). Figure 3A in the application, as filed, reveals that normal tissues are mostly negative for *TCL-1b*. *TCL-1b* transcripts were detected in the testis and placenta but only after several days of exposing the Northern Blot to X-ray

film (page 15, lines 16-17 and see Figure 3C). Likewise, *TCL-1b* transcripts were detected in hematopoietic tissues only *following several days exposure* of the Northern Blot to the X-ray film (italics added) (page 15, lines 16-17 and see Figure 3A). By contrast, Figures 3C and 3D in the application, as filed, show that *TCL-1b* is activated in a T-cell leukemia cell line with a translocation at 14q32.1, the location of the *TCL-1b* gene, (page 16, lines 15-17) compared with the normal bone marrow and with EBV transformed lymphoblastiod B cell lines expressing *TCL1*. While Figure 4A in the application, as filed, reveals that *TCL-1b* is expressed in the spleen, tonsil, fetal liver, fetal kidney, fetal thymus, placenta, kidney, and fetal spleen, transcripts were detected only by semi-quantitative RT-PCR. PCR is much more sensitive than Northern analysis, and will, therefore, detect very low levels of transcripts, which are undetectable by Northern analysis. Malignant cells express *TCL-1b* at a much higher level and are thus the *TCL-1b* expression is readily detected by Northern analysis in these cells.

The specification is enabling

The Examiner cites Pekarsky et al. as teaching that "[n]either the *in vivo* function of Tcl1 nor the mechanism(s) of its oncogenic potential is known." Knowledge of the *in vivo* function and/or mechanism by which oncogenesis is induced is not a requirement for satisfying the enablement requirement of §112, paragraph one. "The enablement requirement refers to the requirement of 35 U.S.C. 112, first paragraph that the specification describe how to make and how to use the invention. The invention that one skilled in the art must be enabled to make and use is that defined by the claim(s) of the particular application or patent." MPEP §2164

The function of Tcl-1b, as well as other members of the Tcl1 family of proteins, is as a transporter of small molecules (page 24, lines 9-12). The present invention relates to nucleic acid sequences and the encoded protein and protein fragments of Tc-1b, not Tcl1. Although there are structural similarities among the members of the Tcl1 family of proteins, there are also significant structural differences. While all members of the Tcl1 family of proteins contain the

hydrophobic core region, the Tcl-1b proteins show a 14 amino acid (page 14, line 20) insertion from Arg44 to Glu58 in SEQ ID NO: 39 (page 21, lines 5-6) that forms a surface accessible flexible loop. The conserved charged residues in the insert loop of Tcl-1b play a significant role in mediating interactions with other proteins or ligands (page 24, lines 5-18). Furthermore, the finding that the human *TCL1b* gene is expressed in syncytiotrophoblasts implies a function in early embryogenesis (page 24, lines 2-4).

"As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The identification of *TCL-1b* is described in the specification under the heading "The Tcl-1b . . . Coding Sequences", beginning on page 28, line 18. The isolation of RNA, the reverse transcription of the RNA into cDNA, and the amplification of the cDNA is described on page 11, lines 7-13. Although sequencing nucleic acid has been a standard laboratory procedure for over 20 years, and therefore well known to those skilled in the art, page 13, lines 9-17 outlines the sequencing protocol.

Claims 1-5 and 8 relate to the isolated nucleic acid (genomic and cDNA), or fragments thereof, and to isolated nucleic acid sequences (cDNA) encoding the Tcl-1b protein, or fragments thereof. Claims 9-12 relate to a recombinant DNA vector encoding Tcl-1b and a host cell containing the vector. The 128 amino acid sequence encoded by the 1.2 kb *TCL-1b* cDNA is shown in SEQ. ID. NO: 39 (see Figure 1 in the application, as filed). It contains a starting ATG codon at position 28 within a perfect Kozak consensus sequence. It is well known, and standard molecular biology, how to transcribe, *in vitro*, the cDNA nucleic acid sequence (SEQ ID NO: 38) into the corresponding RNA and the subsequent translation of the RNA into the amino acid sequence of the encoded protein (SEQ ID NO: 39). Alternatively, the cDNA may be cloned into any one of the expression systems detailed in the current disclosure (beginning on page 34 under the heading "Expression Systems"), with the subsequent translation into the encoded protein.

The claimed invention also encompasses isolated nucleic acid(s) that encode a fragment of Tcl-1b. The disclosure of the genomic and cDNA nucleotide sequences (SEQ ID NO: 40 and SEQ ID NO: 38, respectively) allows those skilled in the art to readily isolate a fragment of *TCL-1b* or its cDNA. This fragment subsequently can be expressed using any one of the expression vector/ host systems disclosed in the specification (*supra*). Alternatively, the polynucleotide can be translated *in vitro* using methods that are well known to those skilled in the art.

Claims 13 and 14 relate to an isolated nucleic acid that is capable of hybridizing to the *TCL-1b* cDNA (SEQ ID NO: 38) or the sequence that is complementary to the *TCL-1b* cDNA. The disclosure of the nucleic acid sequences of the *TCL-1b* cDNA (SEQ. ID. NO: 38) allows those skilled in the art to make an isolated nucleic acid that is capable of hybridizing to the *TCL-1b* cDNA or its complement (*supra*). An isolated nucleic acid capable of hybridizing to the *TCL-1b* cDNA, or its complement, are used, for example, as a probe to isolate a complete *TCL-1b* cDNA or *TCL-1b* genomic clone, as disclosed on page 28, lines 14-17. Another example of the use of an isolated nucleic acid capable of hybridizing to *TCL-1b* cDNA (the deoxynucleotide version of the mRNA sequence) or its complement is to detect and measure *TCL-1b* expression (page 48, lines 11-32 through page 49, lines 1-2, and *infra*). Additionally, the hybridization conditions in which the isolated nucleic acid hybidizes to the *TCL-1b* cDNA, or its complement, are described in the specification on page 29, lines 25-32 through page 30, lines 1-6 (see *supra*).

Host cells containing a vector wherein the cDNA sequence, or fragments thereof, are cloned for subsequent expression of the encoded Tcl-1b, or fragments thereof, are also encompassed by the present invention. In the section entitled "Expression Systems" (beginning on page 34) the Applicant has detailed a number of expression systems that may be used. The Applicant, therefore, has more than complied with the requirement for enablement wherein "the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim . . . ". *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Efficacy of antisense therapeutics

The Examiner, citing Benet et al., states "[r]egarding therapy . . . the art teaches that the efficacy of therapeutics is dependent upon factors such as solubility of the drug, bioavailability at the target site, attainment of effective plasma concentrations, solubility in tissues, biotransformation, toxicity, proteolytic degradation, immunological inactivation, rate of excretion or clearance (half-life), deactivation by the liver, hydrolysis in serum, [and] binding to plasma protein."

Claims 15-16 relate to an antisense nucleic acid that is complementary to at least six nucleotides of *TCL-1b* coding sequence. The Applicant has disclosed what is meant by antisense oligonucleotide sequences on page 56, lines 10-19. Furthermore, on page 57, lines 14-24, the Applicant has disclosed the preparation of antisense nucleic acids. The expression systems detailed in the specification (beginning on page 34 under the heading "Expression Systems", see *supra* and on page 63, lines 17-32 through page 64, lines 1-3, *infra*) further disclose preparation of a host cell containing a vector that will express an antisense nucleic acid, as defined in claim 23.

The success of *in vivo* antisense therapeutics is testimony to antisense efficacy. The Applicant refers to Akhtar and Agrawal "In Vivo Studies with Antisense Oligonucleotides" in *Trends in Pharmacol. Sciences*, 18: 12-18 (1997) wherein the authors disclose many specific examples of *in vivo* efficacy in animal models, as well as ongoing human clinical trials, with oligonucleotides. A fairly detailed understanding of the pharmacokinetic properties of oligonucleotide therapeutics has been published by a number of groups. Briefly, the distribution of oligonucleotides to the tissues occurs very rapidly, plasma half-lives are less than one hour. Moreover, various modifications to nucleic acids protect the molecule from proteolytic digestion and hydroloysis, thereby increasing the intracellular stability. Examples of such modifications can be found in the specification on page 57, lines 25-30. The Examiner is referred to the following references for a fully detailed description of the mechanisms of organ uptake and cellular localization: Cossum, P.A., et al., *J. Pharmacol. Exp. Ther.* 267: 1181-1190, 1993; Cossum, P.A., et al., *J. Pharmacol. Exp. Ther.* 269: 89-94, 1994;

Agrawal, S., et al., *Proc. Natl. Acad. Sci.,* 88: 7595-7599, 1991; Temsamani, J., et al., *Antisense Res. Dev.* 3: 277-284, 1993; Sands, H., et al., *Mol. Pharmacol.* 45: 932-943, 1994 and Saijo, Y., et al., *Oncol. Res.* 6: 243-249, 1994.

Following localization to the target tissue the nucleic acid is taken up by the cells. To be effective, intact oligonucleotides must reach the cytoplasm and then the nucleus. Nuclear pores do not represent a barrier to nuclear localization.

Receptors or channels for nucleic acid uptake have been identified on a variety of cells. It is common knowledge to those skilled in the art that cellular uptake of nucleic acids is by endocytosis (Loke, S.L., et al., "Characterization of Oligonucleotide Transport into Living Cells", *Proc. Natl. Acad. Sci. USA* 86: 3474-3478, 1989). The most efficient mechanism of vesicular endocytotic uptake is by receptor-mediated endocytosis. For example, de Diesbach, et al. (*Nucleic Acids Res.* 28: 868-874, 2000 and the references contained therein), identified a new membrane protein that acts as an oligonucleotide receptor on liver cells. Further, Hanss, et al. (*Proc. Natl. Acad. Sci. USA* , 95: 1921-1926, 1998) have identified a cell membrane nucleic acid channel on kidney cells that conducts nucleic acids into the cell. In addition, Benimetskaya, et al. (*Nature Medicine,* 3: 414-420, 1997) have identified a cell-surface receptor on white blood cells for oligonucleotides that mediates their internalization. Specific receptors for oligonucleotide uptake into mammalian cells is well known in the art, as further exemplified by Yakubov, et al. in 1989 (*Proc. Natl. Acad. Sci. USA,* 86: 6454-6458). This publication also reports the endocytic uptake of oligonucleotides as well as oligonucleotide stability in both the cytoplasm and nuclei. These results, by various investigators dating back to at least 1989, reveal that it is well known in the art that the uptake of oligonucleotides into the cells does occur such that these oligonucleotides reach their target nucleic acid, with the subsequent inhibition of gene expression.

Once inside the cytoplasm (*supra*) the oligonucleotide must enter the nucleus and hybridize to the target nucleic acid. The mechanism of action of nuclear entry also has been studied, and it is generally believed that nucleic acids enter, and exit, the nucleus via nuclear pores. The ability to find and bind

the target site and simultaneously avoid non-specific binding, that is to hybridize to the target nucleic acid within the nucleus, is a prerequisite for downregulation of the target nucleic acid. The Examiner is referred to Politz, et al., *Proc. Natl. Acad. Sci. USA*, 95, 6043-6048, 1998 and also to Politz, et al., *Nucleic Acids Res.*, 23: 4946-4953, 1995 for a detailed biochemical disclosure on the intranuclear hybridization of oligonucleotide to target nucleic acid.

How to use the invention

The Examiner states that "there are no teachings in the disclosure as to how to administer any of an antisense molecule, the protein product, an antagonist of the protein, or an antibody directed against the protein, in order to achieve therapeutic benefit against a particular disease". The Applicant respectfully submits that there are no claims drawn to an antagonist of the protein or an antibody directed against the protein. The claims currently pending relate to nucleic acids encoding Tcl-1b, as well as the protein product itself (i.e. Tcl-1b). On page 57, lines 31-32 through page 58, lines 1-5 the specification discloses administration of "nucleic acid into cells or tissues." Additionally, the specification discloses production of antisense nucleic acids intracellularly (page 63, lines 17-32 through page 64, lines 1-3). Furthermore, on page 58, beginning on line 26, the specification discloses "[v]arious delivery systems . . . to administer a Therapeutic of the invention." The explicit details of the administration protocols are not disclosed, as "[a] patent need not teach, and preferably omits, what is well known in the art." *In re Buchner,* 929 F.2d 660, 661, 18 USPQ2d (Fed. Cir. 1991). *Hybritech, Inc. v. Monoclonal Antibodies, Inc.,* 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986). "Detailed procedures for making and using the invention may not be necessary if the description of the invention itself is sufficient to permit those skilled in the art to make and use the invention." MPEP §2164.

The Examiner further states that "There are no working examples teaching administration of any of the claimed nucleic acids as therapeutics." "Compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, [however,]does not turn on whether an example is disclosed. An example may

be 'working' or 'prophetic'. . . . A prophetic example describes an embodiment of the invention based on predicted results rather than work actually conducted or results actually achieved". MPEP 2164.02. The Applicant has clearly met the requirement of 35 U.S.C. 112, first paragraph, in describing embodiments of the invention (*supra*). "[T]he absence of working examples will not by itself render the invention non-enabled. . . . [L]ack of evidence that the claimed invention works as described should never be the sole reason for rejecting the claimed invention on the grounds of lack of enablement." MPEP §2164.02.

The Examiner states that the "applicant's disclosure lacks guidance as to how to use [the invention as claimed] for diagnosis or therapy of disease." The Applicant respectfully disagrees. Under the heading "Diagnostic Uses," beginning on page 47 of the Application, as filed, the Applicant discloses detection of diseases resulting from chromosome 14 abnormalities, indicating a T-cell malignancy in the patient, by using nucleic acids which are hybridizable to *TC-L1b* mRNA, or its complement, for detection and measurement of *TC-L1b* expression (see page 48, lines 9-32 through page 49, lines 1-2). Specific examples of such hybridization assays can be found on page 50, lines 20-26 of the application. These assays are standard molecular biology techniques, and are thus well known to those skilled in the art. As stated in MPEP §2164 "the specification describe[s] how to make and how to use the invention. ...in such terms that one skilled in the art can make and use the claimed invention . . . [and] to ensure that the invention is communicated to the interested public in a meaningful way. . . . sufficient to inform those skilled in the relevant art how to both make and use the claimed invention. Detailed procedures for making and using the invention may not be necessary."

Additional diagnostic uses of the nucleic acid sequences claimed are disclosed under the heading "Genetic Analysis," beginning on page 44. Nucleic acid probes are used in a polymerase chain reaction, for example, to amplify a *TCL1b* sequence and determine the genetic structure for the presence of a chromosome 14 abnormality, in particular a 14q32.1 abnormality. Again, methodologies to perform such analysis are well known to those in the art.

The nucleic acid encoding Tcl-1b, or fragment thereof, is used in generating a Tcl-1b protein, or fragment thereof, for the generation of antibodies to Tcl-1b. These antibodies are used diagnostically to detect the presence of Tcl-1b in patient samples (page 52, line 24 through page 53, line 25), using methods well known to those of skill in the art, for example Western Blot analysis and immunoprecipitation (page 43, lines 22-23).

Therapeutic uses for the nucleic acids of the invention are detailed in the specification (page 55, 31-32 through page 56, lines 1-9). Antisense nucleic acids are administered to a patient in need of therapy (page 57, lines 31-32 through page 58, lines 1-3 and under the heading "Therapeutic/Prophylactic Methods and Compositions") in order to inhibit the expression of aberrant *TCL-1b* (i.e. due to a chromosome 14 abnormality, particularly 14q31.2). Thus, it is the Applicant's belief that the disclosure teaches those skilled in the art how to make and use the invention, as claimed, and that claims 1 and 9 and amended claims 2-5, 8, 10-16, 23 and 29 are fully enabled, as defined by §112, first paragraph.

It is the Applicant's belief that claims 1 and 9 and amended claims 2-5, 8, 10-16, 23 and 29 are described in the specification to enable those of skill in the art, as defined by 35 U.S.C. §112, first paragraph, and the Applicant respectfully requests reconsideration of claims 1 and 9 and amended claims 2-5, 8, 10-16, 23 and 29. It is the Applicant's belief that claims 1 and 9 and amended claims 2-5, 8, 10-16, 23 and 29 distinctly claim the subject matter that the Applicant regards as the invention, as defined by 35 U.S.C. §112, paragraph two. The Applicant respectfully requests that claims 1 and 9 and amended claims 2-5, 8, 10-16, 23 and 29 be reconsidered in light of the current Response. Prompt consideration and allowance of claims that claims 1 and 9 and amended claims 2-5, 8, 10-16, 23 and 29 are earnestly solicited.

Should the Examiner determine that any further action is necessary to place this application into even better form, she is encouraged to telephone the Applicants undersigned representative at the number listed below.

Respectfully submitted,

CROCE, Carlo

6/26/02
Date

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